Agency for Healthcare Research and Quality
Advancing Excellence in Health Care

NATIONAL GUIDELINE CLEARINGHOUSE

General

Guideline Title

American Gastroenterological Association Institute guideline on the role of elastography in the evaluation of liver fibrosis.

Bibliographic Source(s)

Lim JK, Flamm SL, Singh S, Falck-Ytter YT, Clinical Guidelines Committee of the American Gastroenterological Association. American Gastroenterological Association Institute guideline on the role of elastography in the evaluation of liver fibrosis. Gastroenterology. 2017 May;152(6):1536-43. [19 references] PubMed

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

NEATS Assessment

National Guideline Clearinghouse (NGC) has assessed this guideline's adherence to standards of trustworthiness, derived from the Institute of Medicine's report Clinical Practice Guidelines We Can Trust.

= Poor = Fair = Good = Very Good = Excellent

Assessment	Standard of Trustworthiness
NO	Disclosure of Guideline Funding Source
	Disclosure and Management of Financial Conflict of Interests
	Guideline Development Group Composition
UNKNOWN	Multidisciplinary Group

YES	Methodologist Involvement
▮▮▮▯▯	Patient and Public Perspectives
	Use of a Systematic Review of Evidence
▮▮▮▮▮	Search Strategy
▮▮▮▮▯	Study Selection
▮▮▮▮▮	Synthesis of Evidence
	Evidence Foundations for and Rating Strength of Recommendations
▮▮▮▮▮	Grading the Quality or Strength of Evidence
▮▮▮▮▮	Benefits and Harms of Recommendations
▮▮▮▮▮	Evidence Summary Supporting Recommendations
▮▮▮▮▮	Rating the Strength of Recommendations
▮▮▮▮▮	Specific and Unambiguous Articulation of Recommendations
▮▮▮▯▯	External Review
▮▮▮▮▮	Updating

Recommendations

Major Recommendations

Definitions for the quality of evidence (High, Moderate, Low, Very low) and strength of recommendation (Strong, Conditional) are provided at the end of the "Major Recommendations" field.

Questions 1 and 2

Should vibration-controlled transient elastography (VCTE) vs aspartate aminotransferase to platelet ratio index (APRI) be used to diagnose cirrhosis in adults with chronic hepatitis C?

Should VCTE vs fibrosis-4 index (FIB-4) be used to diagnose cirrhosis in adults with chronic hepatitis C?

Recommendation

In patients with chronic hepatitis C, the American Gastroenterological Association (AGA) Institute recommends VCTE, if available, rather than other nonproprietary, noninvasive serum tests (APRI, FIB-4) to detect cirrhosis. (Strong recommendation, moderate quality evidence)

Question 3

In adults with hepatitis C virus (HCV) undergoing VCTE, at what liver stiffness cutoff can clinicians accurately diagnose cirrhosis (and initiate downstream management), obviating the need for liver biopsy?

Recommendation

In patients with chronic hepatitis C, the AGA suggests a VCTE cutoff of 12.5 kPa to detect cirrhosis. (Conditional recommendation, low-quality evidence)

Question 4

In adults with HCV who have achieved sustained virologic response (SVR) with antiviral therapy undergoing VCTE, at what liver stiffness cutoff can clinicians accurately rule out advanced fibrosis and consider discharging patients from a dedicated liver clinic?

Recommendation

In noncirrhotic patients with HCV who have achieved SVR after antiviral therapy, the AGA suggests a post-treatment vibration controlled transient elastography cutoff of 9.5 kPa to rule out advanced liver fibrosis. (Conditional recommendation, very-low-quality evidence)

Comment: Noncirrhotic patients with VCTE <9.5 kPa who place a low value on the inconvenience and risks of continued laboratory and fibrosis testing, and a high value on avoiding the small risk of developing HCC, may reasonably select to continue specialty care rather than being discharged from the specialty clinic.

Questions 5 and 6

Should VCTE vs APRI be used to diagnose cirrhosis in adults with chronic hepatitis B?

Should VCTE vs FIB-4 be used to diagnose cirrhosis in adults with chronic hepatitis B?

Recommendation

In patients with chronic hepatitis B, the AGA suggests VCTE rather than other nonproprietary noninvasive serum tests (i.e., APRI and FIB-4) to detect cirrhosis. (Conditional recommendation, low-quality evidence)

Question 7

In adults with HBV undergoing VCTE, at what liver stiffness cutoff can clinicians we accurately diagnose cirrhosis, obviating the need for liver biopsy?

Recommendation

In patients with chronic hepatitis B, the AGA suggests a VCTE cutoff of 11.0 kPa to detect cirrhosis. (Conditional recommendation, low-quality evidence)

Questions 8 and 9

Should VCTE vs APRI be used to diagnose cirrhosis in adults with nonalcoholic fatty liver disease (NAFLD)?

Should VCTE vs FIB-4 be used to diagnose cirrhosis in adults with NAFLD?

Recommendation

The AGA makes no recommendation regarding the role of VCTE in the diagnosis of cirrhosis in adults with NAFLD. (No recommendation—knowledge gap)

Question 10

In adults with chronic alcoholic liver disease undergoing VCTE, at what liver stiffness cutoff can clinicians accurately diagnose cirrhosis, obviating the need for liver biopsy?

Recommendation

In patients with chronic alcoholic liver disease, the AGA suggests a VCTE cutoff of 12.5 kPa to detect cirrhosis. (Conditional recommendation, low-quality evidence)

Question 11

In adults with suspected compensated cirrhosis undergoing VCTE, at what liver stiffness cutoff can clinicians accurately rule out high-risk esophageal varices, obviating the need for routine endoscopic screening?

Recommendation

In patients with suspected compensated cirrhosis, the AGA suggests a VCTE cutoff of 19.5 kPa to assess the need for esophagogastroduodenoscopy to identify high risk esophageal varices. (Conditional recommendation, low-quality evidence)

Comment: Patients, particularly those at higher risk, with VCTE <19.5 kPa who place a low value on the inconvenience and risks of endoscopy, and a high value on avoiding the small risk of acute variceal hemorrhage associated with VCTE values of <19.5 kPa, may reasonably select to undergo screening endoscopy.

Question 12

In adults with suspected chronic liver disease undergoing elective nonhepatic surgery, at what VCTE-identified liver stiffness cutoff can clinicians accurately rule out clinically significant portal hypertension (identified as presence of any esophageal varices), potentially minimizing the need for routine invasive testing for portal hypertension (endoscopy, hepatic venous pressure gradient measurement)?

Recommendation

In patients with suspected chronic liver disease undergoing elective nonhepatic surgery, the AGA suggests a VCTE cutoff of 17.0 kPa to detect clinically significant portal hypertension to inform preoperative care. (Conditional recommendation, low-quality evidence)

Comment: Patients, particularly those at higher risk, with VCTE <17.0 kPa who place a low value on the inconvenience and risks of interventions (endoscopy, hepatic venous pressure gradient measurement) to detect clinically significant portal hypertension, and a high value on avoiding the small risk of operative morbidity and mortality associated with elective non hepatic surgery, may reasonably select to undergo screening endoscopy.

Question 13

Should magnetic resonance elastography (MRE) vs VCTE be used to diagnose cirrhosis in adults with chronic hepatitis C?

Recommendation

In adult patients with chronic hepatitis C, the AGA suggests using VCTE rather than MRE for detection of cirrhosis. (Conditional recommendation, very-low-quality evidence)

Question 14

Should MRE vs VCTE be used to diagnose cirrhosis in adults with NAFLD?

Recommendation

In adults with NAFLD and a higher risk of cirrhosis, the AGA suggests using MRE, rather than VCTE, for detection of cirrhosis. (Conditional recommendation, low-quality evidence)

In adults with NAFLD and a lower risk of cirrhosis, the AGA makes no recommendation regarding the role of MRE or VCTE for detection of cirrhosis. (No recommendation—knowledge gap)

Comment: High-risk populations are NAFLD with advanced age; obesity, particularly central adiposity; diabetes; alanine elevated >2x upper limit of normal with an estimated cirrhosis prevalence of 30% (typically seen in a referral setting); low-risk population are those with NAFLD and signs of fatty liver on

imaging only and an estimated cirrhosis prevalence of ≤5% (typically seen in a primary care setting).

Definitions

Grading of Recommendations Assessment, Development and Evaluation (GRADE) Definitions of Quality/Certainty of the Evidence

High	The Committee is very confident that the true effect lies close to that of the estimate of the effect.
Moderate	The Committee is moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low	The Committee's confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect.
Very low	The Committee has very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect.

GRADE Definitions on Strength of Recommendation

	Wording in Guideline	**For the Patient**	**For the Clinician**
Strong	"The AGA recommends..."	Most individuals in this situation would want the recommended course of action and only a small proportion would not.	Most individuals should receive the recommended course of action. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.
Conditional	"The AGA suggests..."	The majority of individuals in this situation would want the suggested course of action, but many would not.	Different choices will be appropriate for different patients. Decision aids may well be useful helping individuals making decisions consistent with their values and preferences. Clinicians should expect to spend more time with patients when working towards a decision.

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Liver fibrosis or cirrhosis related to chronic liver diseases (chronic hepatitis C, chronic hepatitis B, nonalcoholic fatty liver disease [NAFLD], chronic alcoholic liver disease, or suspected compensated cirrhosis)

Guideline Category

Diagnosis

Evaluation

Risk Assessment

Technology Assessment

Clinical Specialty

Gastroenterology

Internal Medicine

Intended Users

Advanced Practice Nurses

Physician Assistants

Physicians

Guideline Objective(s)

To provide clinicians with evidence-based guidance on the specific role of vibration-controlled transient elastography (VCTE) in clinical practice

Target Population

Adults with chronic liver diseases including chronic hepatitis C, chronic hepatitis B, nonalcoholic fatty liver disease (NAFLD), chronic alcoholic liver disease, or suspected compensated cirrhosis

Interventions and Practices Considered

1. Use of vibration-controlled transient elastography (VCTE) versus aspartate aminotransferase to platelet ratio index (APRI), fibrosis-4 index (FIB-4), or magnetic resonance elastography (MRE) for diagnosis of cirrhosis
2. Establishing specific VCTE cutoffs for significant or advanced liver fibrosis or cirrhosis

Major Outcomes Considered

- Overall diagnostic performance of vibration-controlled transient elastography (VCTE) compared with other commonly used, nonproprietary, noninvasive biomarkers or magnetic resonance elastography (true positives [TP], false positives [FP], true negatives [TN], and false negatives [FN] rates) for detection of cirrhosis in different illustrative clinical scenarios, corresponding to variable observed prevalence of cirrhosis depending on practice setting and population in which the test was applied
- TP, FP, TN, and FN rates as surrogate outcomes with inferred downstream consequences on patient important outcomes
- Minimizing rates of FN (i.e., patients incorrectly being labeled as not having the condition, when they actually have the condition) with reasonable rates of TP, FP, and TN
- A balance of FN and FP (i.e., patients incorrectly labeled as having the condition, when they actually do not have the condition)

Methodology

Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

Formulation of Clinical Questions

Through an iterative process, the participants for the technical review developed focused clinical questions deemed relevant for clinical practice that the guideline would address and that related to the diagnostic performance and utility of vibration-controlled transient elastography (VCTE) in 5 different populations: adults with hepatitis C virus (HCV), hepatitis B virus (HBV), nonalcoholic fatty liver disease (NAFLD), chronic alcoholic liver disease, and chronic liver disease (CLD) suspected to have portal hypertension. From these focused questions, well-defined statements in terms of patients, intervention, comparator, and outcome (PICO) were defined, and these formed the framework for formulating the study inclusion and exclusion criteria and guided the literature search. The American Gastroenterological Association Governing Board approved the final set of questions and statements. The focused and PICO questions are shown in Table 1 in the supplementary material of the guideline technical review (see the "Availability of Companion Documents" field). Two questions on the role of magnetic resonance elastography (MRE) on detection of cirrhosis were added after the public comment period.

Search Strategy

To inform evidence pertaining to these focused questions, a systematic literature search of multiple electronic databases on the diagnostic performance of transient elastography in CLDs, was conducted by an experienced medical librarian using a combination of controlled vocabulary supplemented with keywords, with input from the technical review authors. The search was conducted from January 1, 2005 to January 24, 2016, and the databases included: Ovid Medline In-Process & Other Non-Indexed Citations, Ovid MEDLINE, Ovid EMBASE, Ovid Cochrane Database of Systematic Reviews, and PsycINFO. One GRADE (Grading of Recommendations Assessment, Development and Evaluation) methodologist independently reviewed the title and abstract of studies identified in the search, to exclude studies that did not address the focused question, based on pre-specified inclusion and exclusion criteria. The full text of the remaining articles was examined to determine whether it contained relevant information, and relevant articles at end of this process, were reviewed by a second author for appropriateness. Conflicts in study selection at this stage were resolved by consensus, referring back to the original article in consultation with clinical content experts. This search was supplemented with a recursive search of the bibliographies of recently published systematic reviews on this topic, to identify any additional studies. The reviewers restricted the search to English language and human studies. Filters were applied to exclude conference proceedings, editorials, letters to the editor and case reports. Following the public comment period when a decision was made to add two focused questions on diagnostic performance of MRE, an update search of PubMed using key words "magnetic resonance elastography" and "fibrosis" was performed to identify relevant studies.

Study Selection Criteria

There were two broad themes for the focused questions. The first set of questions for each population of interest (HCV, HBV, NAFLD and alcoholic liver diseases) were centered around the overall diagnostic performance (across a broad range of cut-offs) of VCTE in relation to commonly used, non-proprietary, non-invasive serum biomarkers of fibrosis in these conditions (APRI, FIB-4) (PICO# 1, 4, 6). For these questions, the reviewers included randomized controlled trials or observational studies of diagnostic accuracy which met the following inclusion criteria: (a) performed in adults with CLD (corresponding to PICO question), (b) provided adequate description of liver stiffness measurement using VCTE, as well as (c) assessment of fibrosis stage based on liver biopsy as gold standard (for the purposes of this technical review, all histological systems were converted to METAVIR), and (d) provided sufficient data to allow estimation of diagnostic accuracy of VCTE (sensitivity, specificity) for detection of cirrhosis. This

diagnostic performance of VCTE was compared with reported diagnostic performance of corresponding fibrosis biomarkers for detection of cirrhosis, obtained from a recent well-conducted systematic reviews. Since proprietary, serum-based fibrosis markers are expensive and generally have performance comparable to non-proprietary, inexpensive alternatives, the reviewers did not compare the performance of VCTE to other serum-based fibrosis markers.

The second set of focused questions were focused on identifying reliable VCTE-derived liver stiffness cut-offs to either diagnose cirrhosis (PICO# 2, 4, 6, 8), or rule out (PICO# 3) advanced fibrosis or rule out high-risk EV (defined as any medium/large EV, or small varices with high risk stigmata for bleeding) (PICO# 9) or clinically significant portal hypertension (CSPH, defined as presence of any EV) (PICO# 10). Studies included to answer this question were randomized controlled trials or observational studies of diagnostic accuracy which met the following inclusion criteria: (a) performed in adults with CLD (corresponding to PICO question), (b) provided adequate description of liver stiffness measurement using VCTE with cut-off corresponding to diagnosis of cirrhosis, (c) with liver biopsy as gold standard, and (d) provided sufficient data to allow estimation of diagnostic accuracy of VCTE (sensitivity, specificity) for detection of cirrhosis. For these questions, the reviewers *a priori* sought to identify VCTE cut-off maximizing sensitivity (to rule out advanced fibrosis, high-risk EV or CSPH), or maximizing specificity (to diagnose cirrhosis).

For PICO #1–8, VCTE was considered as a test replacement strategy for detection of cirrhosis, that is, in patients with valid results, VCTE would replace routine use of liver biopsy and limit its use to cases with inconclusive VCTE results or diagnostic equipoise. For PICO #9, VCTE was considered as a triage (screening) strategy for upper endoscopy for ruling out high-risk EVs, that is, in patients with liver stiffness below the VCTE-identified threshold, the likelihood of high-risk EVs is sufficiently low to avoid routine upper endoscopy; however, in patients with liver stiffness at or above VCTE-identified threshold, upper endoscopy is warranted to confirm diagnosis before treatment is considered. Likewise for PICO #10, VCTE was considered a triage strategy, that is, patients with liver stiffness below VCTE-identified threshold, clinically significant portal hypertension may be ruled out in risk stratification for elective, nonhepatic surgery; however, in patients with liver stiffness at or above VCTE-identified threshold, further testing (with upper endoscopy or hepatic venous pressure gradient) to evaluate clinically significant portal hypertension may be warranted before a patient is deemed high risk for elective surgery.

Number of Source Documents

Total articles identified: 4577

Total studies included: 79

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Grading of Recommendations Assessment, Development and Evaluation (GRADE) Definitions of Quality/Certainty of the Evidence

High	The Committee is very confident that the true effect lies close to that of the estimate of the effect.
Moderate	The Committee is moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low	The Committee's confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect.

Very low	The Committee has very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect.

Methods Used to Analyze the Evidence

Meta-Analysis

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

Data Abstraction and Risk of Bias Assessment

The following data from each study was abstracted by a single author using a standardized data abstraction form: (a) study characteristics: primary author; time period of study/year of publication; country of study, inclusion and exclusion criteria (to determine population in which the diagnostic performance of vibration-controlled transient elastography (VCTE) has been studied); (b) patient characteristics: age, sex, body mass index, underlying etiology of the chronic liver disease, liver fibrosis stage (stage 0-4, or F0-F4); (c) liver stiffness assessment using VCTE: failure rate, or cut-off corresponding to maximum sensitivity (to rule out cirrhosis, high-risk esophageal varices [EV] or clinically significant portal hypertension [CSPH]), maximum specificity (to diagnose cirrhosis) and cut-off corresponding to best trade-off of sensitivity and specificity corresponding to area-under-the-receiver-operator-curve (AUROC) or Youden index; (d) outcomes reported: presence or absence of cirrhosis, high-risk EV, any EV (as a measure of CSPH) as well as hepatic venous pressure gradient (HVPG)-defined CSPH (HVPG >10mm Hg); (e) test performance of VCTE-derived liver stiffness measurement: sensitivity, specificity, prevalence of outcome of interest in study (to impute numbers of true-positive, true-negative, false-positive, and false-negative results).

The quality assessment of included studies was performed by a single author using the quality assessment of diagnostic accuracy studies (QUADAS) questionnaire, which was designed to assess the internal and external validity of diagnostic accuracy studies included in systematic reviews. This tool is a 14-item instrument that allows for the identification of important design elements in diagnostic accuracy studies such as patient spectrum, the presence or absence of observer blinding and verification bias, handling of indeterminate results, and reporting of patient loss to follow-up evaluation.

Data Synthesis and Statistical Analysis

For the first set of PICOs (patients, intervention, comparator and outcome), comparing overall diagnostic performance of VCTE with other non-invasive markers, pooled summary statistics (and 95% confidence intervals [CI]) for sensitivity and specificity were derived using random-effects model of DerSimonian and Laird, regardless of cut-off in individual studies.

For the second set of PICOs related to identifying reliable cut-offs, as mentioned previously, the reviewers *a priori* sought to identify VCTE cut-off maximizing sensitivity (to rule out cirrhosis, high-risk EV or CSPH), or maximizing specificity (to diagnose cirrhosis). However, during the data abstraction process, the reviewers recognized that variable cut-offs were not consistently reported in included studies; moreover, most studies did not prospectively study a particular cut-off, but rather retrospectively applied the cut-off corresponding to AUROC. Hence, to identify reliable cut-offs, the committee used the most commonly reported cut-off in studies, confirmed their clinical use with content experts (and use in clinical trials which recruited patients with cirrhosis based on VCTE cut-offs), and calculated sensitivity and specificity corresponding to these, as described previously. Though ideally the committee wanted a single cut-off for each PICO, this was not feasible due to variable cut-offs, which were reported in individual studies, and hence, the committee used a narrow range (±1-2kPa) of ideal cut-offs. These cut-offs were:

9.5(±1) kPa to rule out advanced fibrosis or cirrhosis (low false negative [FN] rate) in patients with hepatitis C virus (HCV0
12.5(±1) kPa to diagnose cirrhosis (desired trade-off of false positive [FP] and FN) cirrhosis in patients with HCV
11.0(±1) kPa to diagnose cirrhosis in patients with hepatitis B virus (HBV)
11.0(±1) kPa to diagnose cirrhosis in patients with nonalcoholic fatty liver disease (NAFLD)
12.5(±1) kPa to diagnose cirrhosis in patients with alcoholic liver disease
17.0(±2) kPa to rule out any EV (as a measure of clinically significant portal hypertension) for pre-surgical risk stratification
19.5(±2) kPa to rule out high-risk EV in patients with compensated cirrhosis

Next, using the calculated sensitivity and specificity, the committee calculated rates of true positive (TP), FP, true negative (TN) and FN rates for different clinical scenarios. In addition, using pre-defined illustrative prevalence of outcome, the reviewers estimated positive predictive value (PPV) and negative predictive value (NPV) of a liver stiffness cut-off.

Between-study heterogeneity for all diagnostic test parameters was evaluated initially by graphic examination of Forest plots for sensitivity and specificity. Statistical assessment then was performed using the inconsistency index (I^2), which estimates what proportion of total variation across studies was due to heterogeneity rather than chance; a value of >50% was suggestive of considerable heterogeneity. The reviewers tested for the presence of publication bias by using a regression of the diagnostic log odds ratio against 1/(Effective Sample Size)$^{1/2}$ and weighting according to the effective sample size, with p-value <0.10 indicating significant asymmetry, and suggestive of a significant publication bias.

All analyses were performed using the statistical software Meta-DiSc® (Ramón y Cajal Hospital, Madrid, Spain) (version 1.1.1).

Determination of Maximal Tolerable False Negative Rate - Questionnaire

A pre-meeting questionnaire was administered to both the content experts in the technical review team and the guideline panel to determine their *a priori* maximal tolerable false negative rate for each PICO (i.e., what level of FN rate would they be willing to accept for a particular test, for their patient). As the maximally tolerable rates of false negative tests for any diagnostic strategy is highly context sensitive, the reviewers devised different clinical scenarios with corresponding downstream consequences for each PICO to arrive at fully contextualized estimates of false negative thresholds. A questionnaire was sent to all participants in the clinical guideline panel and technical review team (refer to the Online Supplement for the details of the questionnaire [see the "Availability of Companion Documents" field]).

Quality of Evidence

The quality of evidence was rated using the GRADE approach for diagnostic tests and strategies. In this approach, all evidence from randomized controlled trials (comparing different diagnostic tests or cutoffs of same test) and observational diagnostic accuracy studies start at high-quality, but can be rated down for any of the following factors:

Risk of bias in included studies (inferred based on QUADAS instrument)
Indirectness (present if there are important differences in population studied and those for whom recommendation is being is intended; if cutoffs for VCTE for cirrhosis detection were not prespecified but obtained post-hoc corresponding to AUROC; and if TP, FP, TN, and FN rates are used as surrogates for presumed downstream consequences on patient-important outcomes)
Inconsistency (present if there were considerable differences in the accuracy estimates)
Imprecision (present if there were CIs for TP and FP and TN and FN rates)
Publication bias

In the absence of direct patient-important outcomes from observational diagnostic accuracy studies, surrogate outcomes including TP, FP, TN, and FN were all rated as critical outcomes, and included in evidence profiles.

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

The American Gastroenterological Association (AGA) process for developing clinical practice guidelines incorporates Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology, as outlined by the Institute of Medicine. GRADE methodology was utilized to prepare the background information for the technical review and guideline. Optimal understanding and application of this guideline will be improved by reading applicable portions of the technical review (see the "Availability of Companion Documents" field).

Four members of the guideline panel and AGA support staff met in person with the authors of the technical review on May 20, 2016. The information in the technical review was discussed in a systematic manner facilitating subsequent creation of guideline recommendations addressing each focused question. The strength of each recommendation was rated as either strong or conditional (see the "Rating Scheme for the Strength of the Recommendations" field).

Rating Scheme for the Strength of the Recommendations

Grading of Recommendations Assessment, Development and Evaluation (GRADE) Categories on Strength of Recommendation

	Wording in Guideline	**For the Patient**	**For the Clinician**
Strong	"The AGA recommends..."	Most individuals in this situation would want the recommended course of action and only a small proportion would not.	Most individuals should receive the recommended course of action. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.
Conditional	"The AGA suggests..."	The majority of individuals in this situation would want the suggested course of action, but many would not.	Different choices will be appropriate for different patients. Decision aids may well be useful helping individuals making decisions consistent with their values and preferences. Clinicians should expect to spend more time with patients when working towards a decision.

Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

Method of Guideline Validation

Internal Peer Review

Description of Method of Guideline Validation

This document represents the official recommendations of the American Gastroenterological Association (AGA) on the role of vibration-controlled transient elastography (VCTE) in the evaluation of liver fibrosis. The guideline was developed by the Clinical Guidelines Committee and approved by the AGA Governing

Board.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of evidence is identified and graded for each recommendation (see the "Major Recommendations" field).

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

- Early identification of patients at high risk for progression to decompensated cirrhosis can help direct high-value care and decrease the morbidity and mortality attributed to chronic liver diseases (CLDs). One of the key determinants of progression to CLD-related complications is degree of liver fibrosis, and is often factored in making treatment and surveillance decisions (for hepatocellular cancer and/or esophageal variceal screening).
- With recent recommendations for universal screening for hepatitis C virus (HCV), availability of highly effective but expensive newer direct-acting agents against HCV, and rising prevalence of nonalcoholic fatty liver disease (NAFLD), an increasing number of patients are seeking evaluation for CLDs, and fibrosis staging through noninvasive means has become increasingly important and appealing for physicians. Patients also have a strong preference for vibration-controlled transient elastography (VCTE) over liver biopsy.
- Identifying specific cutoffs for liver stiffness corresponding to cirrhosis and advanced fibrosis could guide management decisions, including treatment for HCV and hepatitis B virus (HBV) and triage for preventive cirrhosis care.

Potential Harms

- False positives (patients incorrectly labeled as having cirrhosis based on vibration controlled transient elastography [VCTE], when actually they do not) may receive unnecessary testing (hepatocellular carcinoma [HCC] surveillance, screening for esophageal varices [EV]) and treatment (longer treatment for hepatitis C virus [HCV]) and have avoidable anxiety, potential testing- or treatment-related complications, and excessive resource utilization.
- False negatives (patients incorrectly labeled as not having cirrhosis based on VCTE, when actually they have cirrhosis) would be falsely reassured, and may not receive appropriate preventive cirrhosis, may receive inappropriate treatment (shorter HCV treatment course), potentially leading to increased morbidity and mortality.
- Misclassification of patients based on VCTE cutoffs

Qualifying Statements

Qualifying Statements

The review of the literature for vibration-controlled transient elastography (VCTE) in patients with liver disease revealed a number of limitations. First, studies used a wide range of cutoffs for VCTE to define

fibrosis stages in chronic liver diseases (CLDs), mostly identified post-hoc corresponding to the area under the receiver operating characteristic (AUROC), and this variability subsequently impacted the quality of evidence. Future studies need to evaluate the performance of standard predefined cutoffs for the different liver diseases. Second, the strength of the VCTE literature is in hepatitis C virus (HCV) but is generally limited to the initial assessment. Many patients with advanced fibrosis and cirrhosis have been or will soon be cured of their HCV, and there is hope that many will see improvement in their fibrosis in time. Their long-term care is currently expected to include surveillance for the complications of portal hypertension and liver cancer for many years. Studies are needed to establish ongoing assessment and determine whether fibrosis (or early cirrhosis) has regressed to the point where ongoing surveillance will no longer be required. However, this will likely require correlation with liver biopsies, as the decrease over time in kPa values alone may, or may not, be related to fibrosis regression, as other factors, such as degree of inflammation or fatty infiltration, may influence liver stiffness. Third, there is major dearth of high-quality evidence in patients with nonalcoholic fatty liver disease (NAFLD). As more patients present for evaluation (including asymptomatic patients incidentally noted to have hepatic steatosis) and therapies are developed for the treatment of NAFLD, clinicians will require effective risk stratification and diagnostic tools to identify patients with progressive fibrosis at risk for complications. Fourth, due to limited data, prospective evaluation of the utility of VCTE as a triage test to evaluate for absence of high-risk esophageal varices (EVs) and ruling our clinically significant portal hypertension before elective surgery is warranted. Finally, although a variety of noninvasive imaging-based fibrosis assessment modalities have been developed, the committee's review focused on VCTE and magnetic resonance elastography (MRE) only; a detailed synthesis of the performance and utility of other noninvasive imaging modalities, such as acoustic radiation force pulse imaging or shear wave elastography, in CLDs, particularly NAFLD, is warranted.

Implementation of the Guideline

Description of Implementation Strategy

An implementation strategy was not provided.

Implementation Tools

Staff Training/Competency Material

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Living with Illness

IOM Domain

Effectiveness

Identifying Information and Availability

Bibliographic Source(s)

Lim JK, Flamm SL, Singh S, Falck-Ytter YT, Clinical Guidelines Committee of the American Gastroenterological Association. American Gastroenterological Association Institute guideline on the role of elastography in the evaluation of liver fibrosis. Gastroenterology. 2017 May;152(6):1536-43. [19 references] PubMed

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2017 May

Guideline Developer(s)

American Gastroenterological Association Institute - Medical Specialty Society

Source(s) of Funding

American Gastroenterological Association Institute

Guideline Committee

American Gastroenterological Association Institute Clinical Guidelines Committee

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Conflicts of Interest

All members were required to complete disclosure a statement. These statements are maintained at the American Gastroenterological Association Institute (AGA) headquarters in Bethesda, Maryland. The authors disclose the following: Dr. Lim has served as a consultant for Bristol Myers-Squibb, Gilead, Merck, and Boehringer-Ingelheim. Dr. Flamm has served as a consultant or received research support from Gilead, Bristol Myers-Squibb, Abbvie, Salix, and Intercept. The rest of the authors disclosed no conflicts related to the content of this guideline.

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Guideline Availability

Available from the Gastroenterology Journal Web site .

Availability of Companion Documents

The following are available:

Singh S, Muir AJ, Dieterich DT, Falck-Ytter YT. American Gastroenterological Association Institute technical review on the role of elastography in chronic liver diseases. Gastroenterology. 2017 May;152(6):1544–77. Available from the Gastroenterology Journal Web site .

Singh S, Muir AJ, Dieterich DT, Falck-Ytter YT. American Gastroenterological Association Institute technical review on the role of elastography in chronic liver diseases. Online supplement. Gastroenterology. 2017 May. 31 p. Available from the Gastroenterology Journal Web site .

AGA process for developing guidelines. 2014 Dec. Available from the American Gastroenterological Association (AGA) Web site .

The AGA Institute process for developing clinical practice guidelines part one: grading the evidence. Clin Gastroenterol Hepatol. 2013 Apr;11(4):329-32. Available from the Clinical Gastroenterology and Hepatology Web site .

In addition, a continuing medical education activity is available from the Gastroenterology Journal Web site .

Patient Resources

None available

NGC Status

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